Disease Risk Calculation Algorithms, CDS Opportunities and Cautions

Kevin S. Hughes, MD, FACS

Co-Director, Avon Comprehensive Breast Evaluation Center

Massachusetts General Hospital

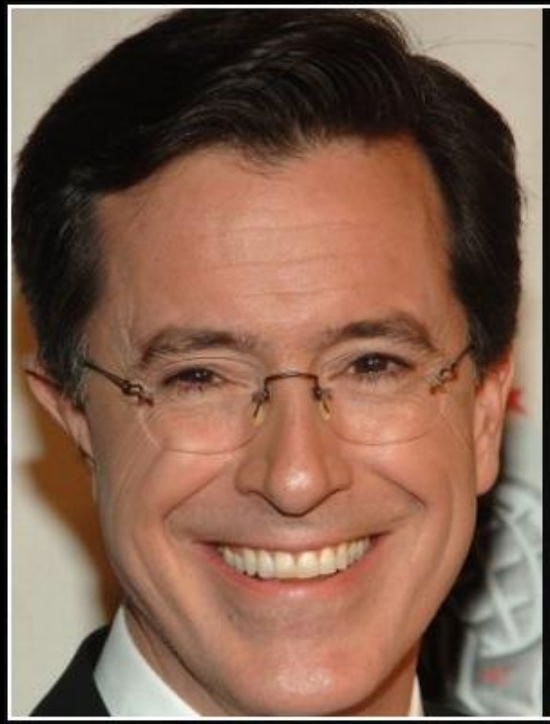
Associate Professor of Surgery

Harvard Medical School

Medical Director

Bermuda Cancer Genetics and Risk Assessment Clinic

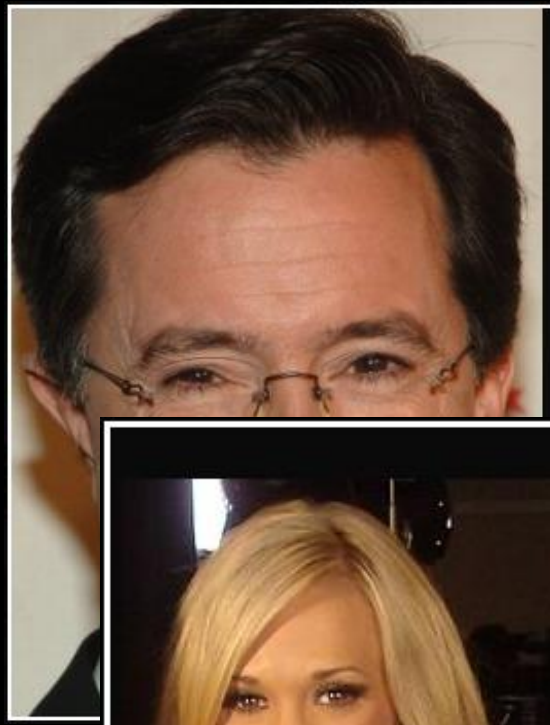
Emiliano Ponzi



Never throw caution to the wind. It could whip back into your eyes and blind you.

— Stephen Colbert —

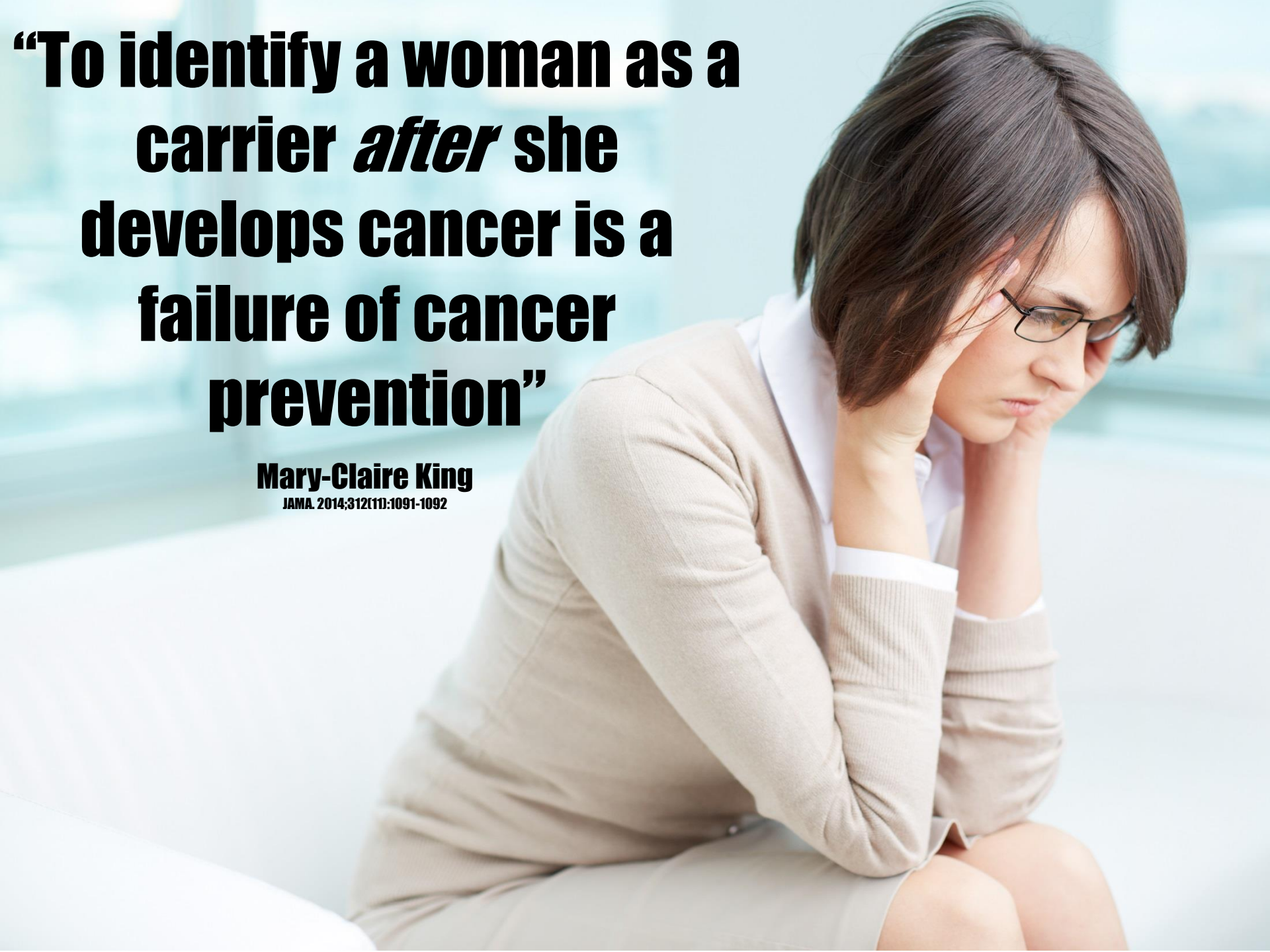
AZ QUOTES



Never throw caution to the wind. It could whip back into your eyes and blind you.

Throw caution to the wind and just do it.

(Carrie Underwood)


“To identify a woman as a carrier *after* she develops cancer is a failure of cancer prevention”
Mary-Claire King
JAMA. 2014;312(11):1091-1092

Many failures of prevention

90% BRCA carriers

99% Lynch carriers

99.9% of everything else

Goal

Identify every mutation carrier for every hereditary syndrome known to man before disease occurs

Table Vs. Pedigree

Mother	**BREAST Cancer age 55**
Maternal Grandfather	**Prostate Cancer age 75**
Sister	**BREAST Cancer age 45**
Brother	**Colon Cancer age 25**
Maternal Aunt	**Cervical Cancer age 33, Ovarian Cancer age 45**
Maternal Cousin (Female)	**Colon Cancer age 30**

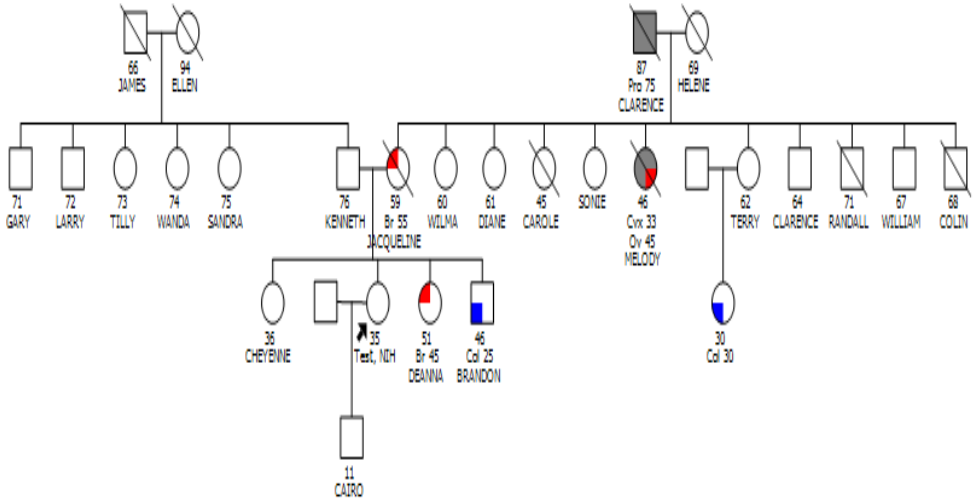
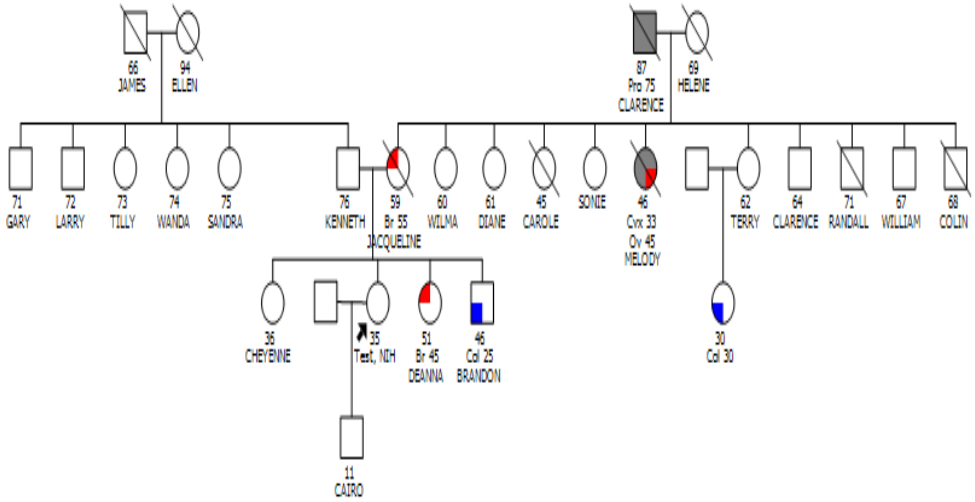


Table Vs. Pedigree

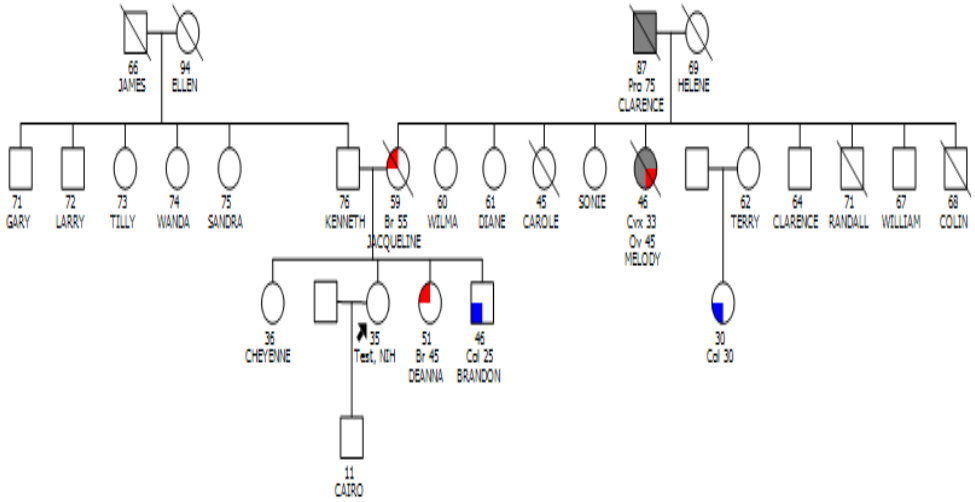
Mother	**BREAST Cancer age 55**
Maternal Grandfather	**Prostate Cancer age 75**
Sister	**BREAST Cancer age 45**
Brother	**Colon Cancer age 25**
Maternal Aunt	**Cervical Cancer age 33, Ovarian Cancer age 45**
Maternal Cousin (Female)	**Colon Cancer age 30**



Neither

Table Vs. Pedigree

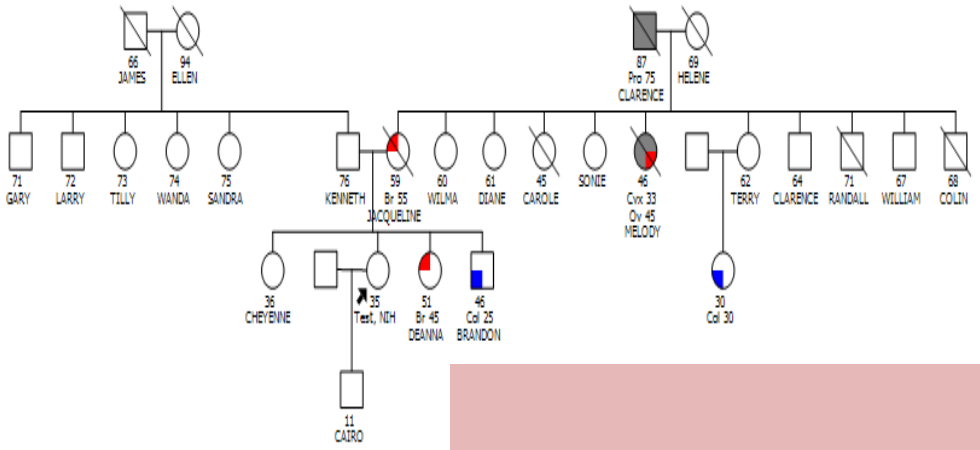
Mother	**BREAST Cancer age 55**
Maternal Grandfather	**Prostate Cancer age 75**
Sister	**BREAST Cancer age 45**
Brother	**Colon Cancer age 25**
Maternal Aunt	**Cervical Cancer age 33, Ovarian Cancer age 45**
Maternal Cousin (Female)	**Colon Cancer age 30**



What Doctors want is to know what to do

CDS

Mother	**BREAST Cancer age 55**
Maternal Grandfather	**Prostate Cancer age 75**
Sister	**BREAST Cancer age 45**
Brother	**Colon Cancer age 25**
Maternal Aunt	**Cervical Cancer age 33, Ovarian Cancer age 45**
Maternal Cousin (Female)	**Col**



BRCAPRO Mutation Risk 25%

Consider Genetic Testing

Arrange consultation

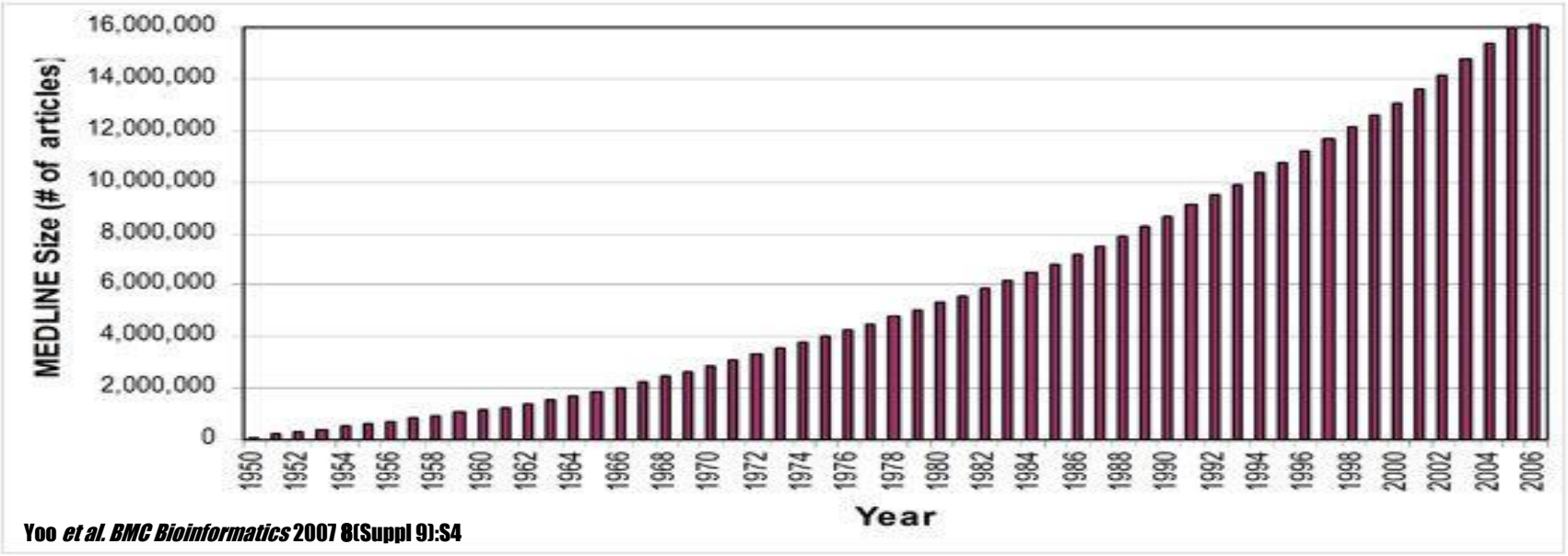
Clinical Decision Support (CDS)

- Apply Models/Guidelines to patient data
  - Identify best course of action
- Results displayed as intuitive ***Visualizations***
- Next steps obvious
- Next steps facilitated

Why do we need CDS?

The human brain is approaching its limit

Knowledge is growing exponentially



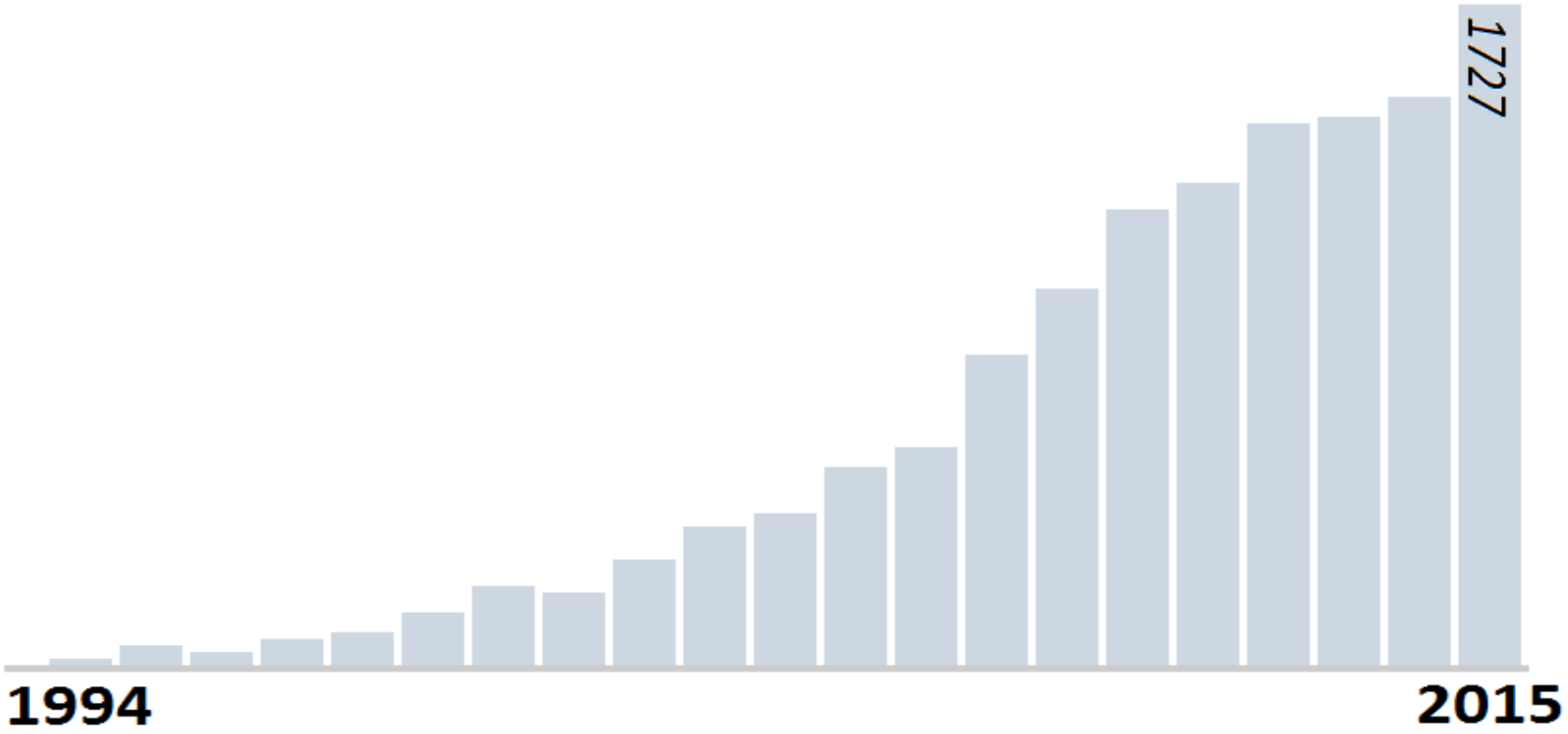
Yoo *et al. BMC Bioinformatics* 2007 8(Suppl 9):S4

Hematologist → Hem/Oncologist → Oncologist → Breast Oncologist

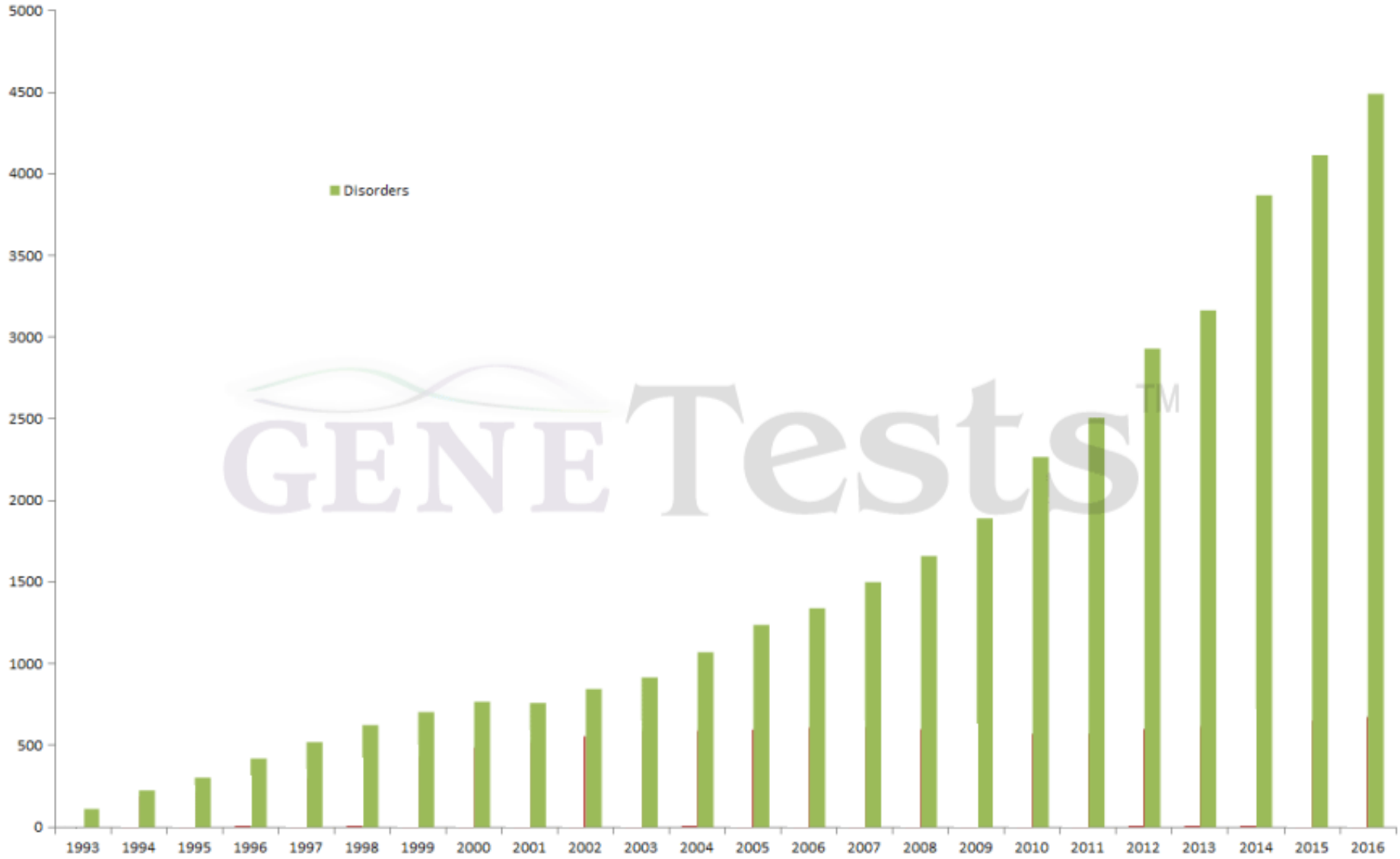
Radiologist → Radiation Oncololgist → Breast Radiation Oncologist

General Surgeon → Surgical Oncologist → Breast Surgeon

Articles about BRCA1



Disorders with genetic tests available



Memory-Based Medicine

"Current medical practice relies heavily on the unaided mind to recall a great amount of detailed knowledge"

Crane, Raymond, The Permanente Journal 7:62, 2003

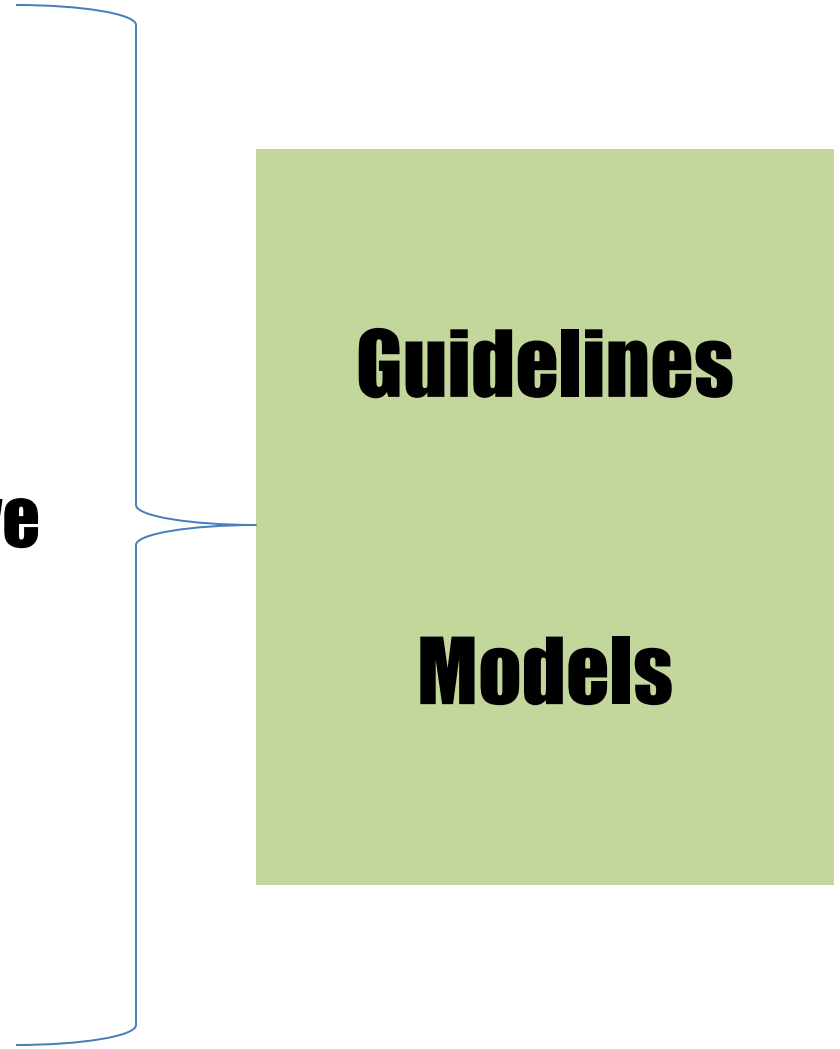
Cancer Genetic Testing

Where is CDS needed?

- ID High risk
- What test
- Characterize the variant
- Prognosis/Penetrance
- Management
- Test relatives

Does patient need a test?

- ID high risk
  - Patient
    - No cancer
    - Past cancer
    - Newly diagnosed cancer
  - Patient and each relative
    - Age
    - Vital Status
    - Cancer status
    - Age diagnosis
    - Ethnicity/Religion
    - Genetic testing



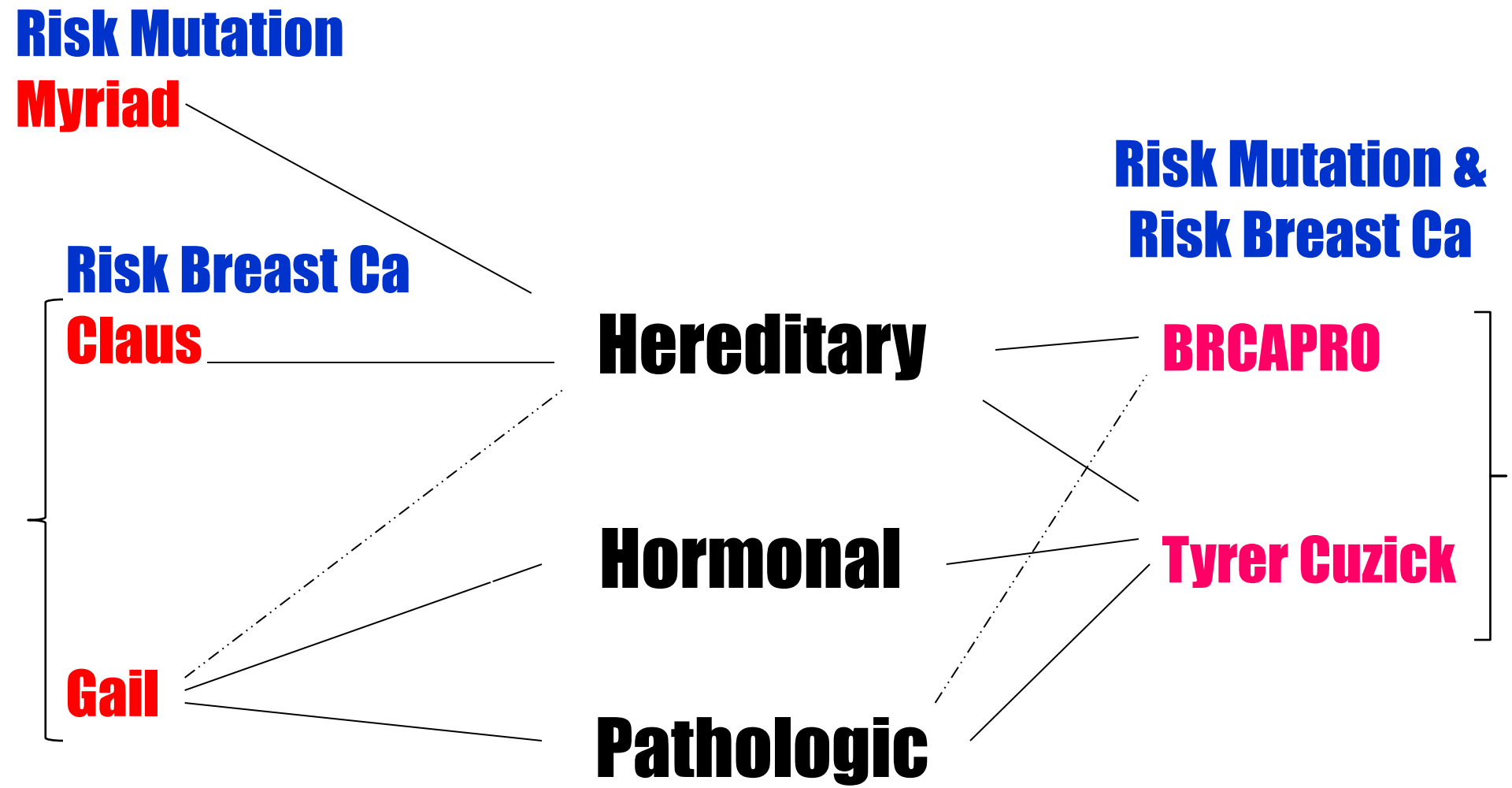
NCCN Guidelines

HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA[a,b,c]

- Individual from a family with a known deleterious *BRCA1*/*BRCA2* mutation
- Personal history of breast cancer[d] + one or more of the following:
  - Diagnosed age ≤45 y
  - Diagnosed any age with ≥1 close blood relative[e] with breast cancer ≤50 y and/or ≥1 close blood relative[e] with epithelial ovarian[f] cancer at any age
  - Two breast primaries[g] when first breast cancer diagnosis occurred ≤ age 50 y
  - Diagnosed age ≤60 y with a triple negative breast cancer
  - Diagnosed age ≤50 y with a limited family history[c]
  - Diagnosed at any age with ≥2 close blood relatives[e] with breast cancer at any age
  - Diagnosed at any age with ≥2 close blood relatives[e] with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age
  - Close male blood relative[e] with breast cancer
  - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[h]
- Personal history of epithelial ovarian[f] cancer
- Personal history of male breast cancer
- Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives[e] with breast and/or ovarian[f] and/or pancreatic or aggressive prostate cancer (Gleason score ≥7) at any age

Family history only

- Clinical judgement should be used to determine if the patient has reasonable likelihood of a mutation, considering the unaffected patient's current age and the age of female unaffected relatives who link the patient with the affected relatives.
- Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.
- Significant limitations of interpreting test results for an unaffected individual should be discussed.
  - First- or second-degree blood relative meeting any of the above criteria
  - Third-degree blood relative with breast cancer[d] and/or ovarian[f] cancer with ≥2 close blood relatives[e] with breast cancer (at least one with breast cancer ≤50 y) and/or ovarian[f] cancer



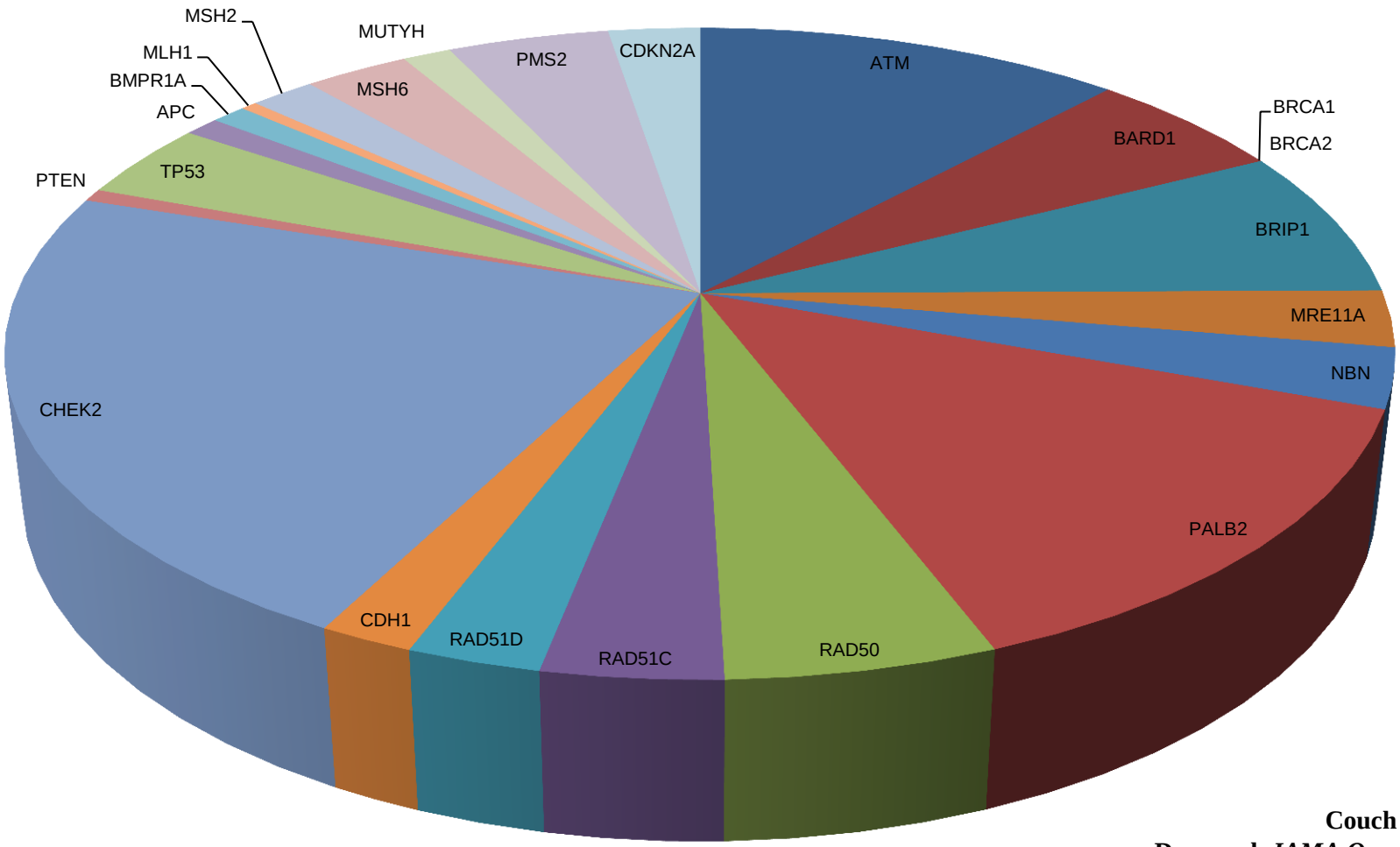
Modified by age, race, ethnicity, religion

What test?

- Which gene or panel?
  - Spectrum of diseases in the family
  - Cost of test
  - Availability
  - Insurers rules


EPCAM
APC
PALB2
CDH1
STK11
BARD1
BRCA1/2
NBN
CHEK2
BRIP1
BMPR1A
MUTYHb
MLH1
MSH2
PTEN
TP53
MSH6
RAD51D
PMS2
RAD51C
ATM
CDKN2A
CDK4
SMAD4

Non-BRCA Mutations



Couch JCO 2015
Desmond. *JAMA Oncology 2015.*
Maxwell *Genetics in Medicine 2014*
Tung *Cancer* 2015 .
Tung JCO 2016
Walsh *PNAS* 2011

Genes have Different Spectrums

Gene	Associated Disease(s)	Adrenal	Brain	Breast	Colorectal	Endometrial	Gastric	Gastrointestinal Stromal Tumor (GIST)	Hepatobiliary	Leukemia / Lymphoma	Lung	Melanoma	Ovarian	Pancreatic	Prostate	Sarcoma	Sebaceous Adenomas/ Carcinomas	Small Bowel	Thyroid	Upper Urinary Tract	Other
		Cancer Sites																			
Breast Cancer Susceptibility																					
ATM (heterozygous)				X										X							
ATM (homozygous)	Ataxia-telangiectasia			X						X				X							
BARD1				X									X								
BRCA1	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)			X									X	X	X						Fallopian tube, Primary peritoneal
BRCA2	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)			X								X	X	X	X						Fallopian tube, Primary peritoneal
BRIP1				X									X								
CDH1	Hereditary Diffuse Gastric Cancer (HDGC)			X	X		X														
CHEK2				X	X								X		X				X	X	
MRE11A				X									X								
MUTYH	MYH-Associated Polyposis (MAP)			X	X	X	X											X			
NBN				X									X		X						
NF1	Neurofibromatosis	X	X	X				X		X											Paragangliomas
PALB2	Familial breast cancer			X									X	X							
PTEN	PTEN Hamartoma Tumor Syndrome (PHTS)			X	X	X						X							X	X	
RAD50				X									X								
RAD51C	Breast-ovarian cancer, familial, 3 (BROVCA3)			X									X								
RAD51D	Breast-ovarian cancer, familial, 4 (BROVCA4)			X									X								
STK11	Peutz-Jeghers Syndrome (PJS)			X	X	X	X				X		X	X				X			Cervical cancer; Testicular cancer
TP53	Li-Fraumeni Syndrome (LFS)	X	X	X	X	X	X			X		X	X	X	X	X				X	

In Press

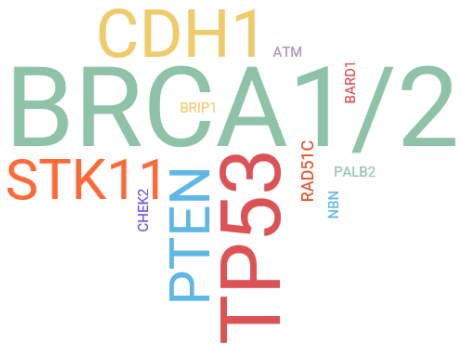
Genes have Different Spectrums

Gene	Associated Disease(s)	Adrenal	Brain	Breast	Colorectal	Endometrial	Gastric	Gastrointestinal Stromal Tumor (GIST)	Hepatobiliary	Leukemia / Lymphoma	Lung	Melanoma	Ovarian	Pancreatic	Prostate	Sarcoma	Sebaceous Adenomas/ Carcinomas	Small Bowel	Thyroid	Upper Urinary Tract
		Cancer Sites																		
Breast Cancer Susceptibility																				
ATM (heterozygous)				X										X						
ATM (homozygous)	Ataxia-telangiectasia			X						X				X						
BARD1				X									X							
BRCA1	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)			X									X	X	X					
BRCA2	Hereditary Breast and Ovarian Cancer Syndrome (HBOC)			X								X	X	X	X					
BRIP1				X									X							
CDH1	Hereditary Diffuse Gastric Cancer (HDGC)			X	X		X													
CHEK2				X	X								X		X				X	X
MRE11A				X									X							
MUTYH	MYH-Associated Polyposis (MAP)			X	X	X	X											X		
NBN				X									X		X					
NF1	Neurofibromatosis	X	X	X				X		X										
PALB2	Familial breast cancer			X									X	X						
PTEN	PTEN Hamartoma Tumor Syndrome (PHTS)			X	X	X						X							X	X
RAD50				X									X							
RAD51C	Breast-ovarian cancer, familial, 3 (BROVCA3)			X									X							
RAD51D	Breast-ovarian cancer, familial, 4 (BROVCA4)			X									X							
STK11	Peutz-Jeghers Syndrome (PJS)			X	X	X	X				X		X	X				X		
TP53	Li-Fraumeni Syndrome (LFS)	X	X	X	X	X	X			X		X	X	X	X	X				X

In Press

Panel Examples

Breast cancer susceptibility



Ovarian cancer susceptibility

No breast risk

PanCancer

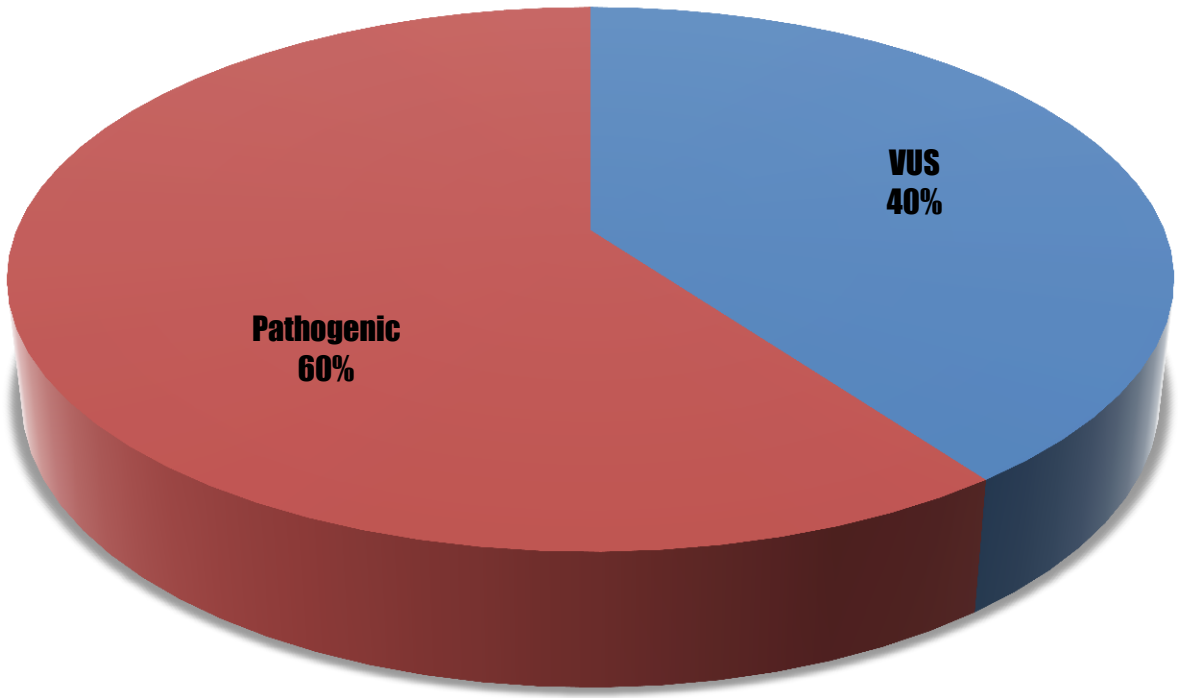
Unrelated to breast or ovarian

Desmond JAMA Oncol 2015

Characterize the variant

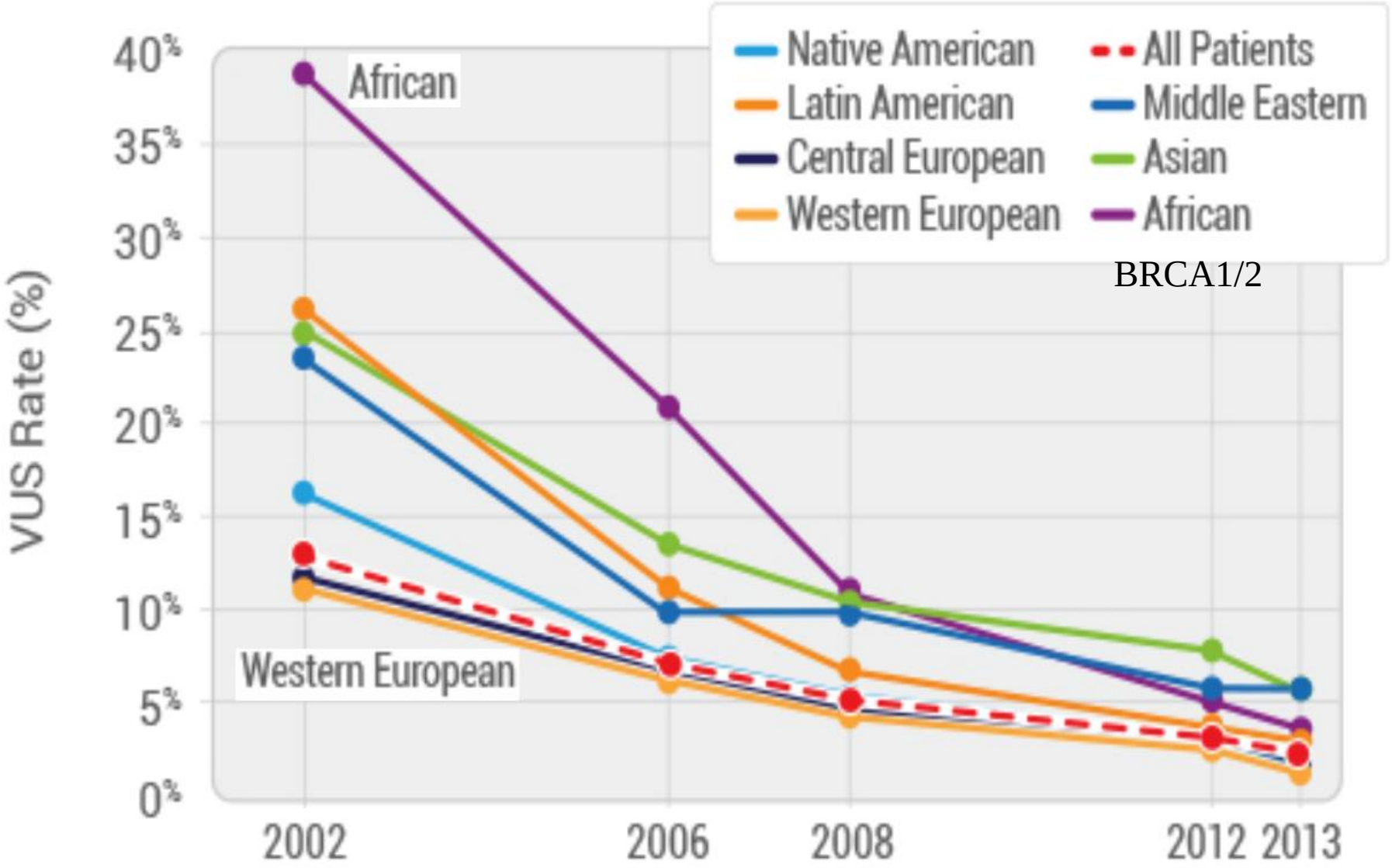
- Significance currently
  - Pathogenic Vs. Benign
- Significance over time
  - VUS

VUS Rate with Panel Testing



Tung *Cancer* 2015

Characterization of VUS' over time

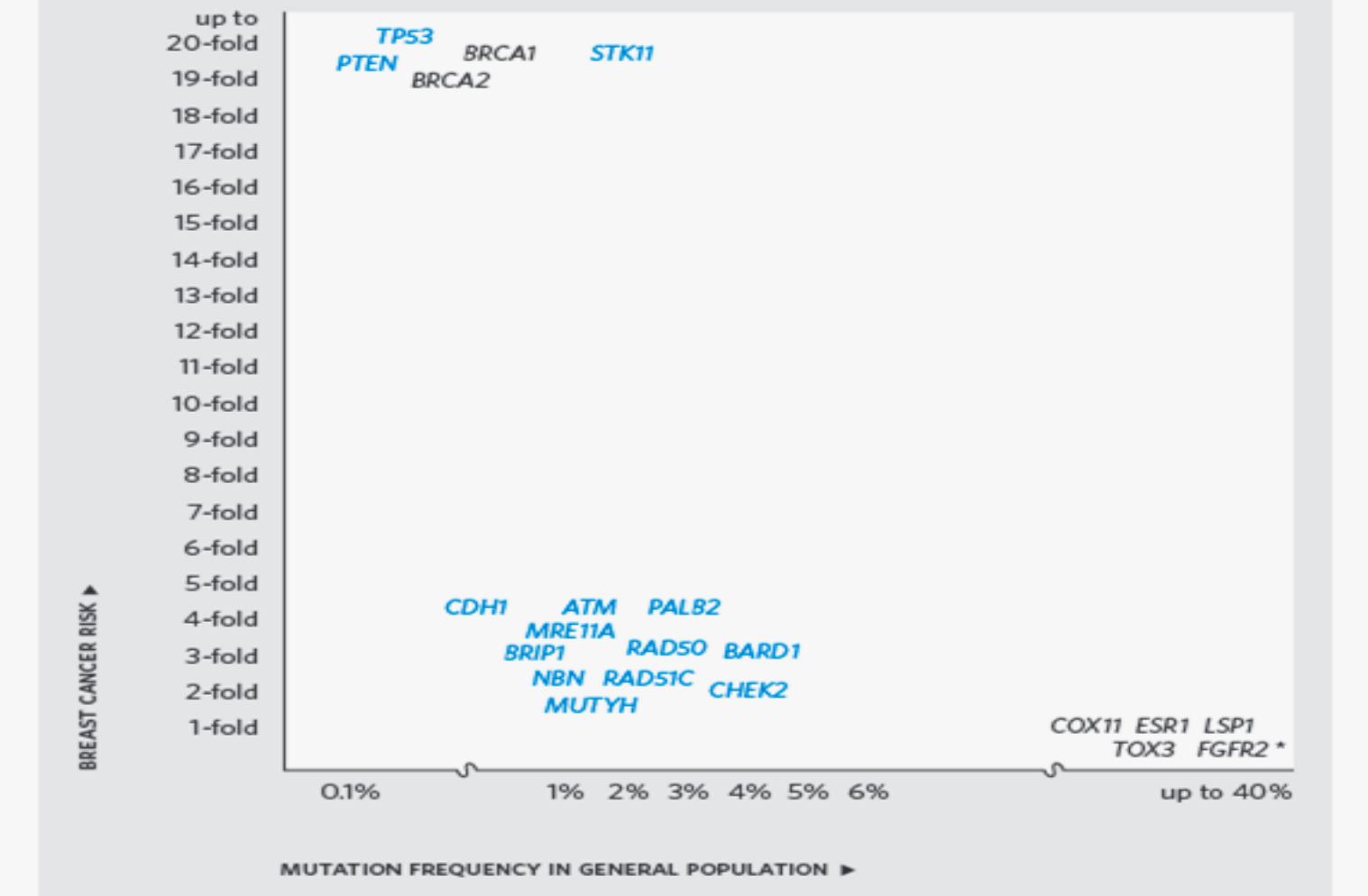


Eggington, J.M., et al. Clin Genet. 2014;86(3):229-37

Prognosis/Penetrance

- Management
  - Spectrum of diseases for that gene
  - Penetrance for each disease

More genes to understand and manage

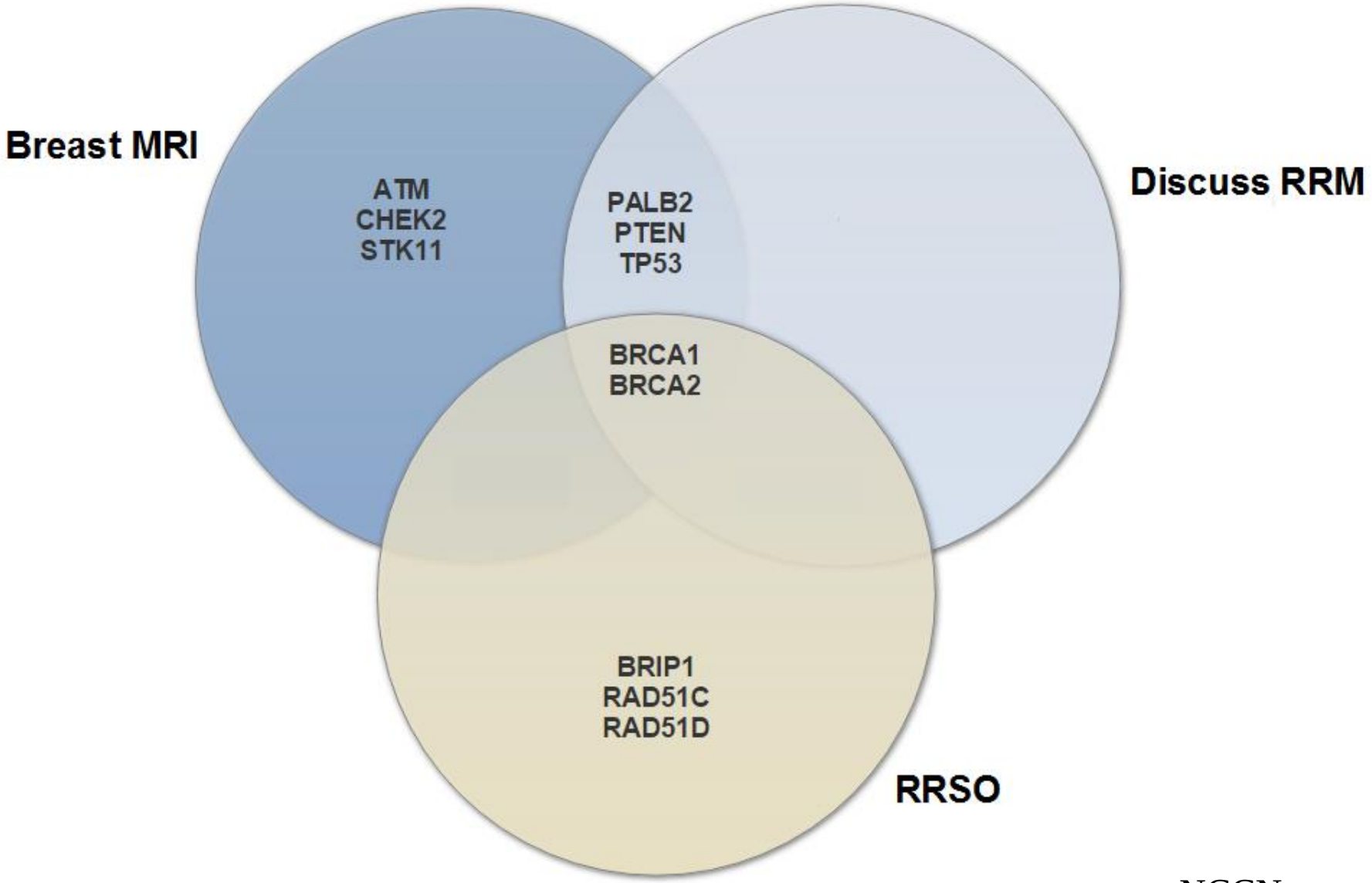


Ambry Genetics

Management

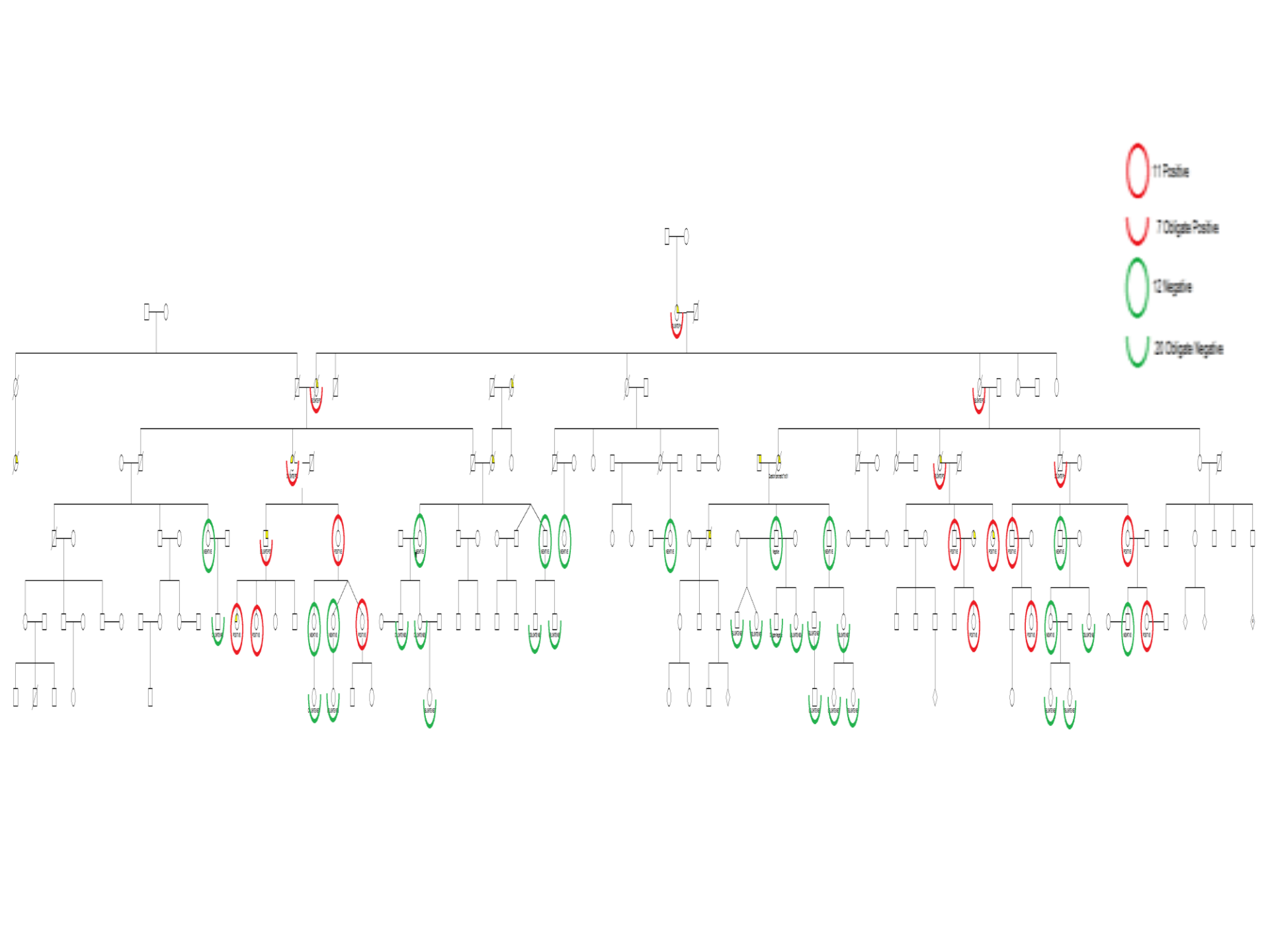
- Spectrum of diseases for that gene
- Penetrance for each disease
- Patient characteristics
  - Age (Chronologic and physiologic)
  - Gender,
  - Presence or absence of cancer
  - Presence or absence of organs

Management varies with Spectrum and Penetrance



NCCN 2016

Test relatives


11 Positive
7 Obligate Positive
12 Negative
28 Obligate Negative

Where is CDS needed?

- ID High risk
- What test
- Characterize the variant
- Prognosis/Penetrance
- Management
- Test relatives

Modular CDS

Data Entry Interface

Knowledge Base

CDS Engine

Algorithms

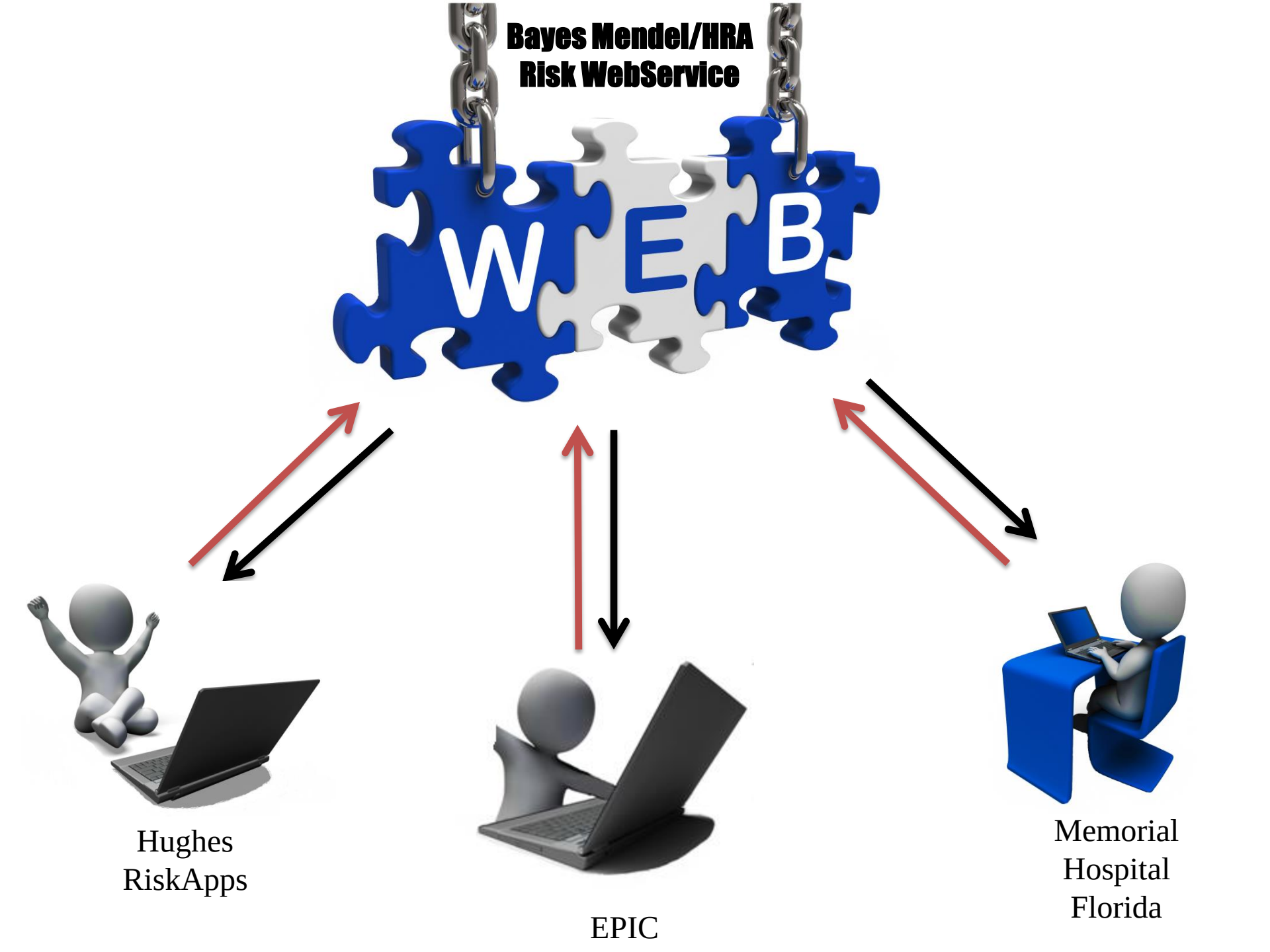
Results Interface

Monolithic EHRs Make No Sense

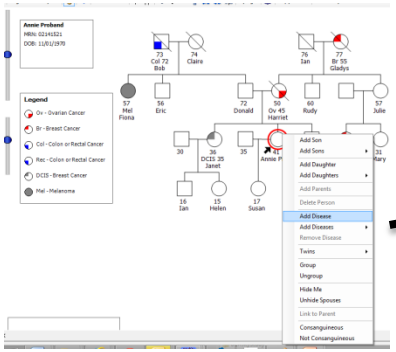
Monolithic EHRs Make No Sense

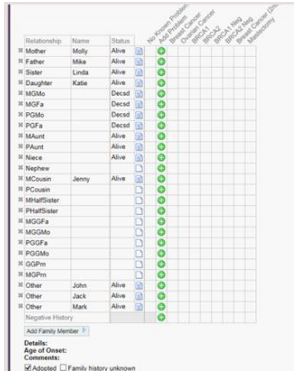
Myriad
BRCAPRO
Gail
Claus
Tyrer Cuzick 6
Tyrer Cuzick 7

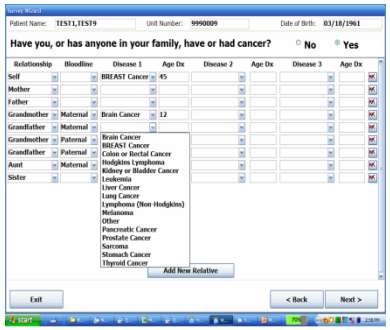
Accepts a single set of data
Runs all models
Update once for all users


Bayes Mendel/HRA
Risk WebService
W E B
Hughes
RiskApps
EPIC
Memorial
Hospital
Florida

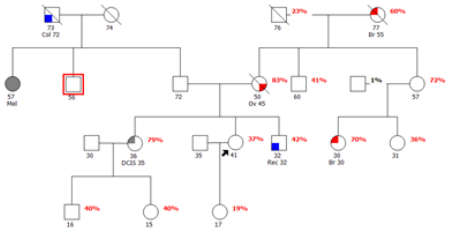
Data Collection Interface

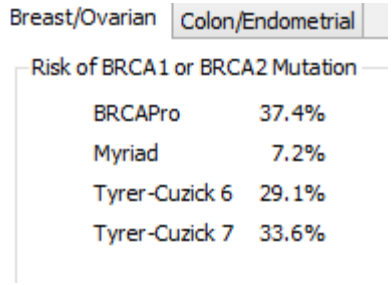


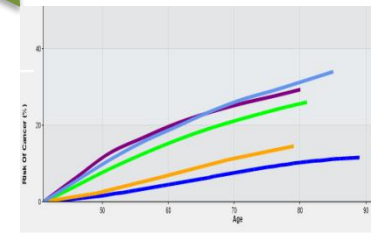




Results Interface







Conclusion

- Accessible Knowledge bases
  - Machine readable guidelines
- Open up EHRs
  - APIs
  - SMART on FHIR
  - Anything